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THE VACCINE THERAPY OF GONOCOCCAL INFECTIONS

Based upon an Address delivered before the Medical Society for the Study of Venereal Diseases on January 23rd, 1925, by PHILIP PANTON, M.B., B.C. (Cantab.).

As a preliminary to our discussion upon the value of vaccine therapy in gonococcal infections I propose to consider very shortly some of the theoretical considerations underlying vaccine therapy in general.

We know that in the case of many infections natural cure is followed by immunity and that this immunity is specific, *e.g.*, scarlet fever, mumps, etc.

We know that parenteral injections of foreign protein, such as dead bacteria or toxins, are followed by demonstrable antibodies, *e.g.*, agglutinins, precipitins, hæmolysins and antitoxins. We have definite evidence that by preventive inoculation, particularly in typhoid, small-pox and anthrax, an immunity may be established.

We have, in my opinion, excellent evidence, in certain bacterial diseases after infection has actually taken place, that the course of the disease may be profoundly modified by vaccine therapy, particularly in a local, superficial and chronic infection, such as that produced by the staphylococcus.

We might argue from these facts that vaccine therapy should be adopted in all forms of bacterial infection, and particularly in a chronic relapsing and localised infection, such as gonorrhœa.

We may, even on these data, attempt to answer a question often put to us by the patient: "If a portion of my body is being invaded by countless living bacteria, what is the good of injecting a comparatively small number of dead ones?" The answer we are in the habit of giving is perhaps to this effect: The infecting agents are localised to a small part of the body and are insufficiently exposed to the defensive mechanisms. The absorption of the toxic products is intermittent, irregular in amount, and possibly in closed foci does not occur at

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all. By giving measured and regularly spaced doses of bacteria under the skin, we ensure the measured absorption by the body generally, and a steady increase in immune substances. We might add—a point I will return to—that the site of bacterial injection, namely the subcutaneous tissues, by most methods of vaccine therapy, plays a very great part in the production of immunity.

These, very briefly, are some of the simple arguments upon which vaccine therapy is based, but it is advisable in our study of immunity that we occasionally pause and ask ourselves if we are really satisfied that our beliefs are sound.

I believe, and I imagine that most of you will agree, that our present conceptions of the exact processes of infection and immunity are crude and often unsound, and I have little doubt that within the next twenty years the whole chapter on immunity will have been rewritten.

Let us reconsider the bases of our faith in the order in which I have mentioned them.

We know that many infections are followed by a specific immunity, and we conclude that cure is brought about by the response of the body to the infection. For what other reason does an infection ever terminate? I will briefly describe some unpublished experiments made by Dr. Benians and myself bearing upon this question. Scarify the skin of a rabbit and rub into the scarified area living pneumococci, an intense inflammation of the skin results, runs a course of three or four days, fades away, the skin desquamates, and the infection is over. Repeat the process, either in the same area of the skin or in another area. The same events occur and can be repeated three or four times, or, so far as I know, indefinitely, with the same result. Here infection takes place, cure following, but no recognisable immunity. Why, then, does the infection come to an end? It is possible that cure follows on changes in the bacteria themselves, changes similar to those which bring about death of bacteria in culture tubes, and we are apt to forget in our consideration of recovery from infection the possibility of intrinsic degeneration of the infecting agents. I should like to mention another experiment. The white mouse is extremely susceptible to pneumococcal infection. Yet if the mouse's skin is treated in the way I have described for the rabbit, nothing visible happens. No apparent infection takes place. Yet

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the mouse thus treated is in some instances relatively immune to subsequent pneumococcal infection. Here we have immunity without infection or reaction. So that we may get infection and cure without immunity, and immunity without infection. The latter experiment might conceivably be explained as an instance of preventive inoculation without visible reaction. I will return to it in a moment.

Our second piece of evidence in favour of vaccine therapy is the appearance in the blood of certain so-called antibodies following natural infection or inoculation. We have rather jumped to the conclusion that these substances are evidences of immunity. Yet it is as well to bear in mind that they may merely be concomitant phenomena, of interest and of value in diagnosis, but not necessarily evidence of immunity at all. This is almost certainly true of agglutinins, the amount of which or the presence of which may be no guide to the amount or absence of immunity.

The value of preventive inoculation, again, is little guide to the value of therapeutic vaccines, since it is reasonable to expect that cure, after infection is established, would be a more difficult matter. Preventive inoculation is most successful when a living virus is used as in vaccinia, or in anthrax with animals, and there is no doubt that immunity response is greater in most cases to living organisms than to organisms killed by heat or otherwise maltreated.

With regard to the value of vaccine therapy in certain bacterial infections, and in particular staphylococcal diseases, I am myself, after some experience, convinced. In other infections, and particular gonococcal infections of the urethra, I am reasonably sure that vaccine therapy as at present practised is of less value. I am not prepared to say, because I have not sufficient evidence, how much value it has, if any. Such evidence must, I think, rest on clinical results, and these should be obtained from the various clinics without difficulty ; but we require very large numbers of cases treated with vaccines and without vaccines under the same conditions and carefully observed before a definite statement can be made. Isolated series of cases treated by this or that kind of vaccine are valueless.

I would like to revert to certain experiments I have

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already partly described, and to consider them from a different angle. But first consider how we give a vaccine. It is most important, and I doubt if any of us realise how important. We pass a hollow needle attached to a syringe through the skin into the subcutaneous tissue and inject a measured amount of a suspension of dead bacteria. In the process we wound the skin and soil the cut surface with a minute amount of the vaccine. The bulk of the vaccine is injected subcutaneously, but is in communication with the skin edge until healing has taken place. Also we carry down into the subcutaneous tissue a minute amount of epithelial tissue. Now consider Besredka's experiments with anthrax in rabbits and guinea pigs. He found that by injecting into the subcutaneous tissue many times the fatal dose of anthrax bacilli without touching the skin nothing happened. But the animal was not subsequently immune to an ordinary subcutaneous dose. He found also that by scarifying the skin and rubbing in virulent bacilli a rapidly fatal infection followed. If, however, devitalised bacilli were first used a reaction only followed, and the animal could be completely immunised. He concluded that anthrax was inoculable only on the skin, and that immunity could only be produced by the skin. That the animal inoculated in the ordinary way with a syringe, as we give a vaccine, died only because the skin was infected in the process.

Dr. Benians and myself have not entirely confirmed these results. We found that large doses of anthrax bacilli in capsules broken under the healed skin led to no evidence of infection, but did produce some degree of immunity, in some cases a very high degree. That an immunity can be produced by infection of the skin alone we also agree.

We further, in a few cases, got the following remarkable results. Rabbits which had previously received two or three capsules broken under the skin without effect, received heavy doses of bacilli given subcutaneously in the ordinary way and survived. They were then scarified and inoculated on the skin without effect. They therefore appeared immune to ordinary subcutaneous inoculation and to skin inoculation. But twelve days after the skin inoculation they again received a subcutaneous dose and died rapidly. It was as if the final skin inoculation had resensitised the animal. But anthrax is peculiarly a skin

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infection, and I will just recall our experiments with the pneumococcus. The rabbit can be infected on the skin and recover, but without developing a skin immunity. The mouse is apparently not susceptible to a dose of pneumococci in the subcutaneous tissue, nor to a dose in the skin, but it invariably dies after the ordinary transcutaneous inoculation.

What bearing have these experiments upon vaccine therapy? I think we have good evidence that infection by the skin and by the subcutaneous tissue are different things, which have been confused because we usually infect both together. That immunity may or may not result from either or both, and that again, by our usual process of inoculation, we have confused the issue.

In our consideration of the value of vaccine therapy I would make the following suggestions. That we might attempt to give our vaccines with more attention to the receptive tissue. We might, for example, get much better results by giving the entire dose intradermally, or we might try to obtain general immunity from both tissues by giving the vaccine with an intradermal needle, and passing the first portion into the layers of the skin and the remainder into the subcutaneous tissue. These proceedings are not the minutiae of technique, they are possibly of fundamental importance.

Then as to the vaccine itself, my impression is that a mixture of two or three strains, or even a single stock strain, will prove as efficacious as an autogenous strain, but that the preparation of the vaccine may be of great importance. Probably the more complicated our process, the less efficacious our result, and in this connection I would like to ask a question of the Society. Why should we not attempt to immunise against gonorrhoea by giving intradermal doses of living bacteria?

In conclusion, I recognise that my suggestions and remarks are of a somewhat colloquial nature, and partly inspired by a piece of research work which is at present far from complete.